Attorney's Docket No.: 13498-009002 / MET-7/Continuation

Applicant: Randall B. Lauffer et al.

Serial No.: 09/887,706

Filed: September 8, 2000

Page : 3 of 14

In the claims:

Please amend the claims as follows:

Claims 1-6/3 (cancelled).

64. (Currently Amended) A method for monitoring treatment of a tissue comprising HSA in a patient, said method comprising:

a) administering a contrast agent to the <u>said</u> patient, the <u>said</u> contrast agent comprising a <u>physiologically compatible metal chelate</u> an <u>organic chelating agent</u> complexed to a paramagnetic metal ion,

wherein said organic chelating agent is selected from the group consisting of DTPA, DOTA, DTPA-BMA, and HP-DO3A;

wherein said organic chelating agent the chelate is covalently bound to a structure: -(L)_m-SDTBM either at a methyl carbon of an acetate chelating moiety of said organic chelating agent or at an ethylene carbon backbone moiety of said organic chelating agent,

wherein L is a physiologically compatible linker and wherein m can be 0 to 4;

wherein <u>said</u> SDTBM is a state dependent tissue binding moiety that comprises one or more zero to six linear or branched alkyl groups having 1 to 10 <u>carbon atoms</u>; zero to five cycloalkyl groups; zero to five aryl groups; or heterocyclic groups or combinations thereof, wherein said alkyl, cycloalkyl, or aryl groups can be optionally and independently substituted with from 1 to 5 ether, carboxylate, or sulfate moieties;

the said contrast agent further having:

- 1) an R1 observed value in a 4.5 wt% solution of HSA at 25 °C of greater than about 10 mM⁻¹ sec⁻¹; and
- 2) a percent binding to HSA in a 4.5 wt%, pH 7.4 solution of HSA of greater than about 10%;



Applicant: Randall B. Lauffer et al.

Serial No.: 09/887,706

Filed

: September 8, 2000

Page

: 4 of 14

b) subjecting the said patient to magnetic resonance imaging to determine an initial signal intensity value in a region of interest of the said undesired tissue;

Attorney's Docket No.: 13498-009002 / MET-

7/Continuation

- c) applying an interventional therapy to at least a portion of the said undesired tissue in order to treat [the] said undesired tissue, the said interventional therapy selected from the group consisting of a thermal energy generation, a cryoablation, an injection of a denaturing liquid, an injection of a chemotherapeutic agent, and a photodynamic therapy; d) contemporaneously monitoring with magnetic resonance imaging a change in the said
- initial signal intensity value in the said region of interest of the said undesired tissue during the said interventional therapy; and
- e) stopping the said interventional therapy application when the said change in the said initial signal intensity value in the said region of interest of the said undesired tissue is more than about a 50% 10% reduction in the said initial signal intensity value.
- The method of claim 64, wherein the said paramagnetic metal ion 65. (Currently Amended) complexed to the metal chelate is selected from the group consisting of Gd(III), Fe(III), Mn(II), Mn(III), Cr(III), Cu(II), Dy(III), Ho(III), Er(III), Pr(III), Eu(II), Eu(III), Tb(III), and Tb(IV)[, and wherein the metal chelate comprises an organic chelating agent].
- 66. (Cancelled).
- (Currently Amended) The method of claim 64, wherein said the organic chelating agent 67. comprises DTPA and wherein the said paramagnetic metal ion complexed to the metal chelate is Gd(III).
- 68-70. (Cancelled).
- (Currently Amended) The method of claim 64, wherein the said SDTBM comprises two 71. to five or more cycloalkyl or aryl groups or combinations thereof and wherein the said two to five or more cycloalkyl or aryl groups or combinations thereof are arranged in a rigid, non-planar orientation.

Applicant: Randall B. Lauffer et al.

Serial No.: 09/887,706

Filed: September 8, 2000

Page : 5 of 14

72. (Currently Amended) The method of claim 71, wherein at least one of the <u>said</u> two <u>to five</u> or more cycloalkyl or aryl groups is a cyclohexyl group.

Attorney's Docket No.: 13498-009002 / MET-

7/Continuation

- 73. (Currently Amended) The method of claim 64, wherein the <u>said</u> R1observed value is greater than about 20 mM⁻¹ sec⁻¹.
- 74. (Currently Amended) The method of claim 73, wherein the <u>said</u> R1observed value is greater than about 30 mM⁻¹ sec⁻¹.
- 75. (Currently Amended) The method of claim 74, wherein the said R1observed value is greater than about 40 mM⁻¹ sec⁻¹.
- 76. (Currently Amended) The method of claim 64, wherein the said percent binding to HSA is greater than about 50%.
- 77. (Currently Amended) The method of claim 76, wherein the said percent binding to HSA is greater than about 80%.
- 78. (Currently Amended) The method of claim 77, wherein the <u>said</u> percent binding to HSA is greater than about 95%.
- 79. (Currently Amended) The method of claim 64, wherein the <u>said</u> tissue is selected from the group consisting of cancerous tissue, tumorous tissue, and neoplastic tissue.
- 80. (Currently Amended) The method of claim 79, wherein the said tissue is cancerous tissue.
- 81. (Currently Amended) The method of claim 64, wherein the <u>said</u> interventional therapy application is [the] <u>said</u> generation of thermal energy, and wherein the <u>said</u> thermal energy is



Applicant: Randall B. Lauffer et al.

Serial No.: 09/887,706

Filed

: September 8, 2000

Page

: 6 of 14

generated by a source selected from the group consisting of one or more focused ultrasound waves, radiofrequency waves, microwaves, and lasers.

Attorney's Docket No.: 13498-009002 / MET-

7/Continuation

(Currently Amended) The method of claim 64, wherein the said physiologically 82. compatible linker L is selected from the group consisting of linear alkyl, branched alkyl, cyclic alkyl, aryl, ether, polyhydroxyl, polyether, polyamine, heterocyclic, peptide, peptoid, phosphodiester, and amide moieties.

(Currently Amended) The method of claim 64, wherein the said contrast agent is selected 83. from the group consisting of MS-315, MS-317, MS-322, MS-323, MS-325, MS-326, MS-327, and MS-328.

(New) The method of claim 64, wherein said reduction is more than about a 50% 84. reduction in said initial signal intensity value.